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## **Interfraction variation in lung tumor position with abdominal compression during stereotactic body radiotherapy**

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## Abstract

**Purpose:** To assess the effect of abdominal compression on the interfraction variation in tumor position in lung stereotactic body radiotherapy (SBRT) using cone-beam computed tomography (CBCT) in a larger series of patients with large tumor motion amplitude.

**Methods:** Thirty patients with lung tumor motion exceeding 8 mm who underwent SBRT were included in this study. After translational and rotational initial setup error was corrected based on bone anatomy, CBCT images were acquired for each fraction. The residual interfraction variation was defined as the difference between the centroid position of the visualized target in three dimensions derived from CBCT scans and those derived from averaged intensity projection images. We compared the magnitude of the interfraction variation in tumor position between patients treated with [ $n=16$  (76 fractions)] and without [ $n=14$  (76 fractions)] abdominal compression.

**Results:** The mean $\pm$ standard deviation (SD) of the motion amplitude in the longitudinal direction before abdominal compression was  $19.9\pm7.3$  (range, 10–40) mm and was significantly ( $p<0.01$ ) reduced to  $12.4\pm5.8$  (range, 5–30) mm with compression. The greatest variance of the interfraction variation with abdominal compression was observed in the longitudinal direction, with a mean $\pm$ SD of  $0.79\pm3.05$  mm, compared to  $-0.60\pm2.10$  mm without abdominal compression. The absolute values of the 95<sup>th</sup> percentile of the interfraction variation for one side in each direction were 3.97/6.21 mm (posterior/anterior), 4.16/3.76 mm (caudal/cranial), and 2.90/2.32 mm (right/left) without abdominal compression, and 2.14/5.03 mm (posterior/anterior), 3.93/9.23 mm (caudal/cranial), and 2.37/5.45 mm (right/left) with abdominal compression. An absolute interfraction variation greater than 5 mm was observed in six (9.2%) fractions without and 13 (17.1%) fractions with abdominal compression.

**Conclusions:** Abdominal compression was effective for reducing the amplitude of tumor motion. However, in most of our patients, the use of abdominal compression seemed to increase the

interfraction variation in tumor position, despite reducing lung tumor motion. The daily tumor position deviated more systematically from the tumor position in the planning CT scan in the lateral and longitudinal directions in patients treated with abdominal compression compared to those treated without compression. Therefore, target matching is required to correct or minimize the interfraction variation.

**Keywords:** Stereotactic body radiation therapy; interfraction variation; abdominal compression; non-small cell lung cancer.

## Introduction

Radiation therapy is a double-edged sword in that it is effective for treating several tumor types, while at the same time creating morbidity. This is particularly true when it comes to the delivery of high-dose hypofractionated treatments to a moving target, as in stereotactic body radiation therapy (SBRT) for lung cancer. Indeed, the better local control and overall survival with recent high-dose radiation techniques might be compromised by movement of the tumor, which could increase the probability of missing the tumor, leading to greater irradiation of surrounding normal tissues, more local failure, and side effects [1, 2]. Consequently, motion management is of great importance for accurate beam delivery in tumors affected by respiratory motion and for reducing doses to the surrounding tissues [3].

Different methods have been used to deal with tumor motion, including increasing the margins to account for the motion, inhibiting respiratory movement with abdominal compression or breath-holding, respiratory gating, and real-time tumor tracking. Whatever method used, it must be reliable and reproducible in order to deliver safe SBRT [4].

Abdominal compression was used in many early SBRT studies and has become a popular motion-management method [5]. It consists of constraining the patient's breathing with a pressurized abdominal cushion or pressure pad [6]. Several studies reported its efficiency at reducing the amplitude of respiratory-induced tumor motion [5, 7]. However, the daily reproducibility of the compression effect of the plate can be undermined by changes in the patient's anatomy and respiratory pattern over the course of the treatment [5].

Recently, the introduction of soft-tissue imaging to the treatment room offers the possibility of daily imaging and online correction of tumor position errors before treatment [8-10]. Using those techniques, several authors evaluated intra- and interfractional variations in tumor motion in patients treated with SBRT for either lung or liver cancer [4, 11-13]. However,

although four-dimensional computed tomography (4D CT) or cone beam CT (CBCT) were used in most of those studies, only a few evaluated the difference in the interfraction variation in tumor position between patients with large motion amplitude treated with and without abdominal compression for lung SBRT. Bissonnette *et al.* reported that patients with abdominal compression demonstrated the greatest variability in tumor motion amplitude and in time spent on the treatment couch. In that series, only three patients out of 12 who underwent 4D CT were treated with abdominal compression, making it difficult to draw any conclusion from their study. Moreover, the range of tumor motion at the planning scan for the majority of the 12 patients did not exceed 5 mm, with the tumors mostly located in the upper and middle lobes [4].

In our institution, a small abdominal pressure plate is used to reduce tumor motion when lung tumor motion observed by x-ray fluoroscopy is  $\geq 8$  mm in the longitudinal direction [7]. Here, we assessed the effect of abdominal compression on the interfraction variation in tumor position in lung SBRT using CBCT in a larger series of patients with a large tumor motion amplitude.

## Materials and Methods

### *Patient population*

Between April 2011 and October 2012, 33 patients with lung tumor motion  $> 8$  mm in the longitudinal direction were treated with SBRT. Of the 33 patients, we retrospectively analyzed 30 [22 males, eight females; median age 79 (range, 49–90) years] who underwent CBCT images prior to beam delivery in each fraction. The fractionation schedules used were 48 Gy in four fractions (19 patients), 56 Gy in four fractions (five patients), 60 Gy in eight fractions (five patients), and 64 Gy in 16 fractions (one patient) normalized to 100% at the isocenter. The tumors were located in the upper lobe in seven, in the middle lobe in two, and in the lower lobe in 21 cases. The patient and treatment characteristics are summarized in TABLE I.

105 **TABLE I.** Patient and treatment characteristics.

	Without compression	With compression
Number of patients	14	16
Sex		
Male/female	10/4	12/4
Age (years), median	76 (range, 49–87)	81 (range, 59–90)
Location		
Right/left	10/4	12/4
Upper/middle/lower lobe	4/2 /8	3/0/13
Motion amplitude (mm), median	10.5 (range, 8–35)	12 (range, 5–30)
Prescription dose		
48 Gy/56 Gy/60 Gy/64 Gy	10/1/2/1	9/4/3/0

*Four-dimensional computed tomography and target delineation*

During simulation, all patients were positioned and immobilized on a BodyFix vacuum cushion (Medical Intelligence, Schwabmünchen, Germany) with both arms raised, and  
 110 underwent an x-ray fluoroscopy evaluation using the Acuity Planning, Simulation, and Verification System, ver. 8.1 (Varian Medical Systems, Palo Alto, CA, USA). When the lung tumor motion observed with x-ray fluoroscopy exceeded 8 mm in the longitudinal direction, the ability of a pressure plate to reduce the tumor motion was tested. The pressure device consisted of a pressure plate (Medical Intelligence) placed 3–4 cm below the costal margin of the ribs  
 115 below the xiphoid. The plate was connected by the means of a graduated screw, to a bar that was firmly attached to the treatment couch at a position that was reproduced at each treatment. The screw was then tightened to compress the plate until sufficient reduction of the motion amplitude was obtained. The position of the screw was recorded and reproduced during each treatment session (Fig. 1). We ensured that the compression could be tolerated over the treatment course.



**Figure 1.** Photograph showing a patient positioned on the treatment couch with the abdominal compression device.

Subsequently, 4D CT was performed under free breathing for the patients treated without abdominal compression or forced shallow breathing for those with abdominal compression using the Varian Real-Time Position Management System, ver. 1.7 (Varian Medical Systems) using a Light Speed RT CT Scanner (General Electric Medical Systems, Waukesha, WI, USA) with a slice thickness of 2.5 mm in axial cine mode [14]. The 4D CT slices and respiratory motion data were transferred to an Advantage 4D workstation (General Electric Medical Systems), in which the maximum intensity projection (MIP) and averaged intensity projection (AIP) were calculated after phase binning of the 4D CT in 10 equally spaced phase bins.

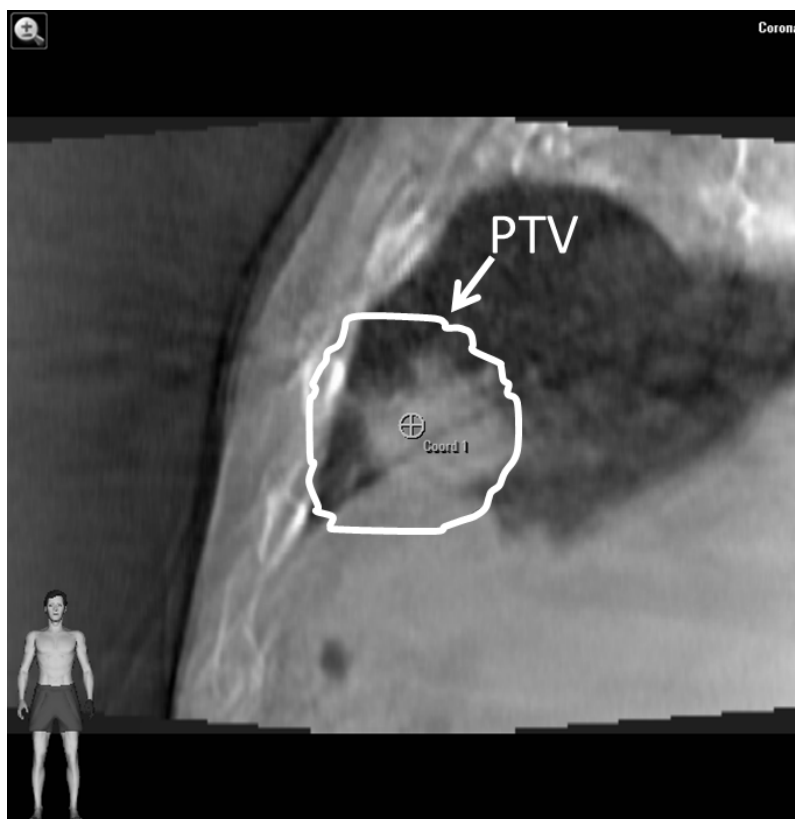


The dataset was imported to the iPlan RT Image system (BrainLAB AG, Feldkirchen, Germany). Internal target volumes (ITVs) were delineated on the MIP using the lung CT window setting. When the ITVs on MIP were found to be insufficient, we manually corrected the ITVs based on an x-ray fluoroscopy evaluation. Planning target volumes were then created by adding 5-mm margins to the ITVs in all directions. The AIP images were transferred to the Vero4DRT system (Mitsubishi Heavy Industries, Ltd., Japan, and BrainLAB, Feldkirchen, Germany) for image registration.

#### 140 *Image guidance and data acquisition*

Patients were treated on the Vero4DRT system equipped with a dual kV x-ray imaging subsystem, electronic portal imaging device, infrared camera system, and robotic treatment couch with five degrees of freedom (three axes of translation and two axes of rotation) for patient set-up correction [15]. Before irradiation, orthogonal radiographic images were acquired and fused with digitally reconstructed planning radiographs based on bony structure using the ExacTrac fusion software (BrainLAB AG). The patient's position was readjusted by moving the robotic couch and O-ring of the Vero4DRT system to correct for both translational and rotational initial setup errors according to the fusion results. Then, a second set of orthogonal radiographic images were acquired for positioning verification to ensure that the residual error was within  $\pm 0.5$  mm and  $\pm 0.2^\circ$  for translational and rotational errors, respectively. Subsequently, the lung tumor position was verified using CBCT images acquired by rotating one set of x-rays and a flat panel-detector in the dual imaging subsystem [16]. The scan time for a  $200^\circ$  gantry rotation was 29 s. The CBCT data were reconstructed in a field of view (FOV) measuring  $215 \times 150$  mm (diameter  $\times$  range) with a slice thickness of 2.5 mm. The centroid position of the visualized target was then automatically determined by the ExacTrac fusion software, and the residual

interfraction variation in the centroid position of the visualized target in three dimensions (3D), derived from CBCT scans relative to the corresponding AIP images was subsequently recorded for 152 fractions by two experienced radiotherapy technicians (Fig. 2). The result of image fusion was reviewed by three experienced radiation oncologists.



**Figure 2.** An example of tumor displacement on CBCT images in the coronal plane. Note that the visualized target is partially outside the PTV in the CBCT image.

### *Data analysis*

The mean and standard deviation (SD) of the lung tumor positional errors were calculated for each patient in the lateral, longitudinal, and vertical directions. From these values, the population systematic error ( $\Sigma$ ) and random error ( $\sigma$ ) were also calculated for each direction. Then, the magnitude of the interfraction variation in tumor position,  $\Sigma$ , and  $\sigma$ , were compared

between the patients treated with and without abdominal compression.

170 Additionally, the mean vector displacement during the treatment course was calculated by averaging the 3D vector displacements in tumor position for each fraction. We then sought the correlation between the mean vector displacements and the motion amplitude in the longitudinal direction obtained from the x-ray fluoroscopy evaluation in patients treated without and with abdominal compression.

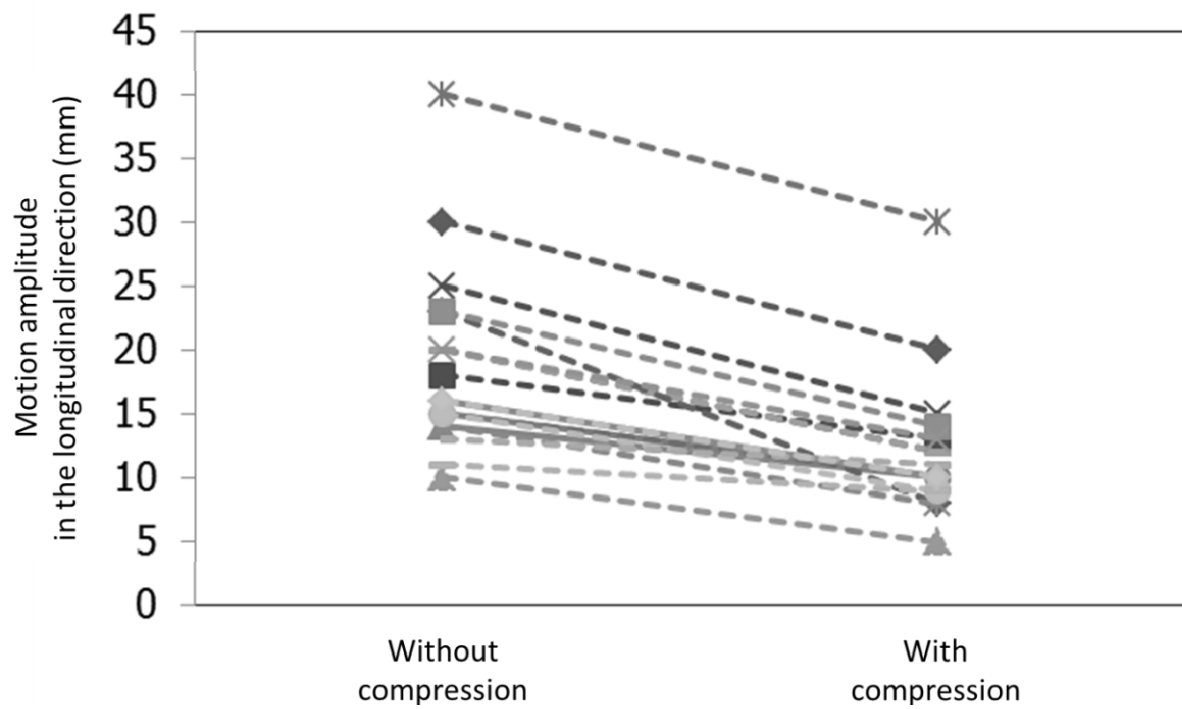
175 Sagittal AIP images were used to evaluate the vertical distance between the centroid position of the visualized target and the edge of the diaphragm (tumor-diaphragm distance). We subsequently assessed the relationship between this distance and the mean vector displacement in the group of patients treated with and without abdominal compression.

Differences were considered significant at  $p < 0.05$ .

## 180 Results

### *Effect of abdominal compression*

Of the 30 patients, the pressure plate was used in 16 (76 fractions). In the 14 (76 fractions) remaining patients, although the respiratory motion observed with x-ray fluoroscopy exceeded 8 mm, abdominal compression was not applied either for medical reasons (abdominal aneurysm in five, gallstones in one, abdominal surgery in one, severe chronic obstructive pulmonary disease in two, and dementia in one), or inability to significantly reduce the amplitude of tumor motion (four patients). The mean $\pm$ SD of the motion amplitude in the longitudinal direction before abdominal compression was 19.9 $\pm$ 7.3 (range, 10–40) mm and was significantly 185 ( $p < 0.01$ ) reduced to 12.4 $\pm$ 5.8 (range, 5–30) mm with compression (Fig. 3). The reduction in 190 tumor motion in the longitudinal direction was significant ( $p < 0.01$ ).



**Figure 3.** Reduction in tumor motion in 16 patients after applying abdominal compression. The reduction in tumor motion in the longitudinal direction was significant ( $p < 0.01$ ).

195 *Interfraction variation in tumor position*

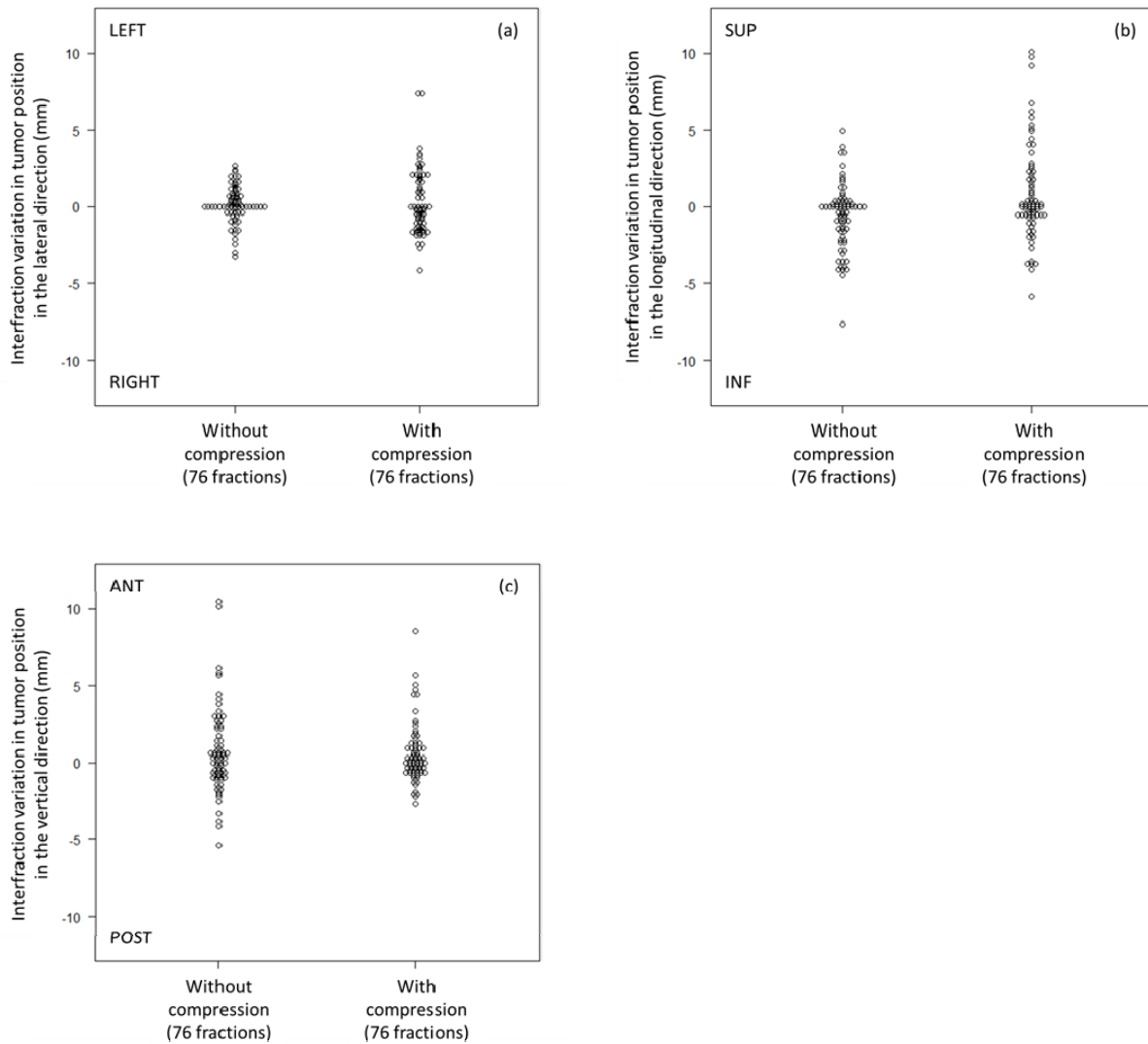
TABLE II summarizes the results of the interfraction variation in tumor position in 3D derived from CBCT scans relative to the corresponding planning AIP images.

**TABLE II.** Interfraction variation in tumor position in 3D for 30 patients.

	Without compression (76 fractions)			With compression (76 fractions)		
	VRT (mm)	LNG (mm)	LAT (mm)	VRT (mm)	LNG (mm)	LAT (mm)
Mean	0.64	-0.60	0.17	0.53	0.79	0.26
SD	2.69	2.10	1.14	1.89	3.05	2.05
Max	10.50	5.03	2.66	8.58	10.06	7.40
Min	-5.33	-7.69	-3.25	-2.63	-5.92	-4.14
$\Sigma$	2.67	1.56	0.83	1.33	2.49	1.79
$\sigma$	1.72	1.79	0.80	1.20	2.19	1.19

200 Abbreviations: VRT=vertical, LNG=longitudinal, LAT=lateral, SD=standard deviation, Max=maximum, Min=minimum,  $\Sigma$ =systematic error,  $\sigma$ = random error.

The largest variance with compression was observed in the longitudinal direction, with a mean $\pm$ SD of 0.79 $\pm$ 3.05 (range, -5.92–10.06) mm, compared to -0.60 $\pm$ 2.10 (range, -7.69–5.03) mm without compression. The interfraction variation was larger with compression than without compression, except in the vertical direction.  $\Sigma$  and  $\sigma$  were larger in patients treated with abdominal compression than in patients treated without abdominal compression in the lateral and longitudinal directions, with the largest values observed in the longitudinal direction. In the vertical direction, however,  $\Sigma$  and  $\sigma$  were smaller in patients treated with abdominal compression. Figure 4 shows the interfraction variation in the lateral (a), longitudinal (b), and vertical (c) directions. The differences in the variances without and with compression were significant ( $p<0.01$ ) in both the vertical and longitudinal directions.



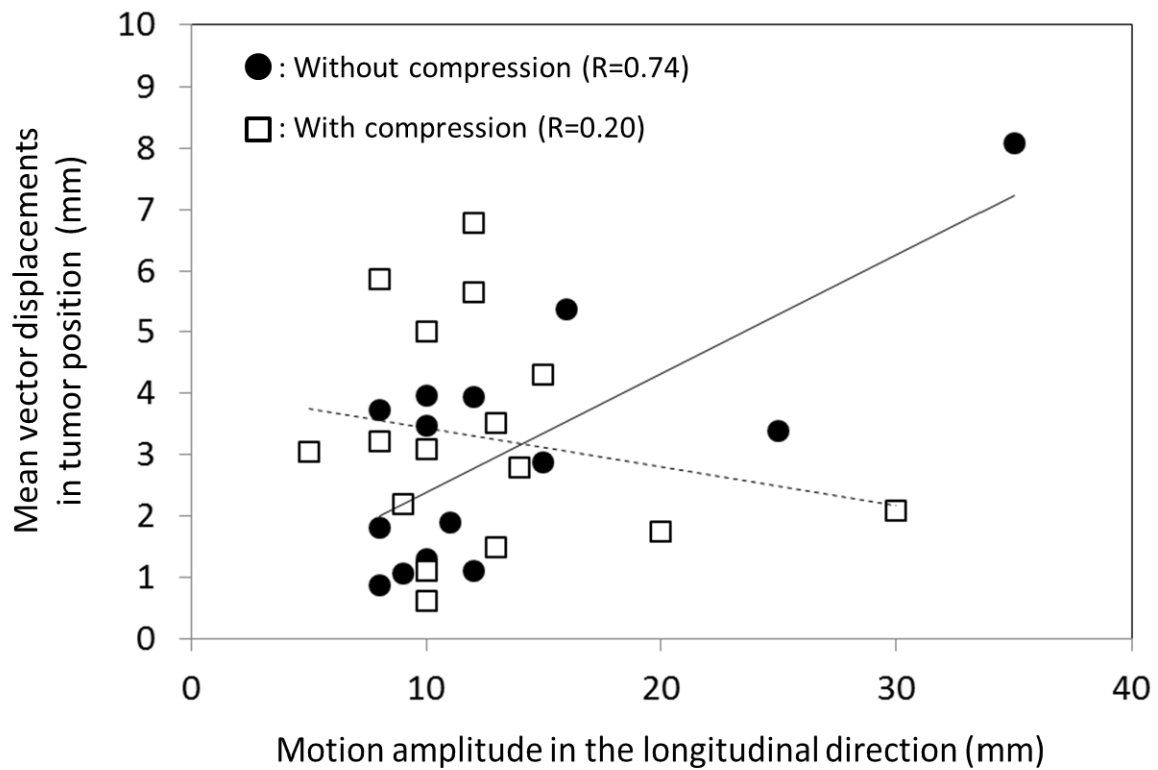
**Figure 4.** Interfraction variation in tumor position without and with abdominal compression in the lateral (a), longitudinal (b), and vertical (c) directions.

The absolute value of the 95<sup>th</sup> percentile of the interfraction variation for one side in each direction was 3.97/6.21 mm (posterior/anterior), 4.16/3.76 mm (caudal/cranial), and 2.90/2.32 mm (right/left) without compression, and 2.14/5.03 mm (posterior/anterior), 3.93/9.23 mm (caudal/cranial), and 2.37/5.45 mm (right/left) with compression. Interfraction variation greater

than 5 mm was observed in three (20.0%) patients without compression and six (40.0%) patients with compression. With abdominal compression, absolute interfraction variation exceeding 5 mm  
225 was observed in two (2.6%), nine (11.8%), and three (3.9%) fractions in the lateral, longitudinal, and vertical directions, respectively.

The motion amplitude in the longitudinal direction was strongly correlated with the mean vector displacement in tumor position in patients treated without abdominal compression ( $R=0.74$ ), while there was no correlation in patients treated with abdominal compression  
230 ( $R=0.20$ ) (Fig. 5).

There was no correlation between the tumor-diaphragm distance and the mean vector displacement in both patients treated without ( $R=-0.19$ ) and with abdominal compression ( $R=0.00$ ).



**Figure 5.** Correlation between the motion amplitude ( $x$ -axis) in the longitudinal direction determined by x-ray fluoroscopy evaluation and the mean vector displacements in tumor position ( $y$ -axis) in patients treated without and with abdominal compression. Regression lines for without and with abdominal compression are shown as solid and broken lines, respectively.

## Discussion

### *Effect of abdominal compression*

The benefit of abdominal compression for reducing respiratory motion in lung cancer patients is well known. Heinzerling *et al.* reported a significant reduction in the tumor motion in the lateral, longitudinal, and overall directions with abdominal compression [5]. Negoro *et al.* reported that abdominal compression reduced the mean lung tumor movement from 12.3 to 7.0



mm [7]. Bouilhol *et al.* reported an efficient reduction in the motion amplitude for lesions close to the diaphragm for lung SBRT treatment, with minor benefits or even unwanted effects such as increased tumor motion and ITV for other locations [17]. In our study, the majority of patients had lower lobe tumors (21 patients). The mean range of motion in the longitudinal direction before abdominal compression was 19.9 mm, which was reduced to 12.4 mm with compression ( $p<0.01$ ) (Fig. 3). This result compared well with previous studies under comparable analysis conditions.

#### *Interfraction variation in lung tumor position*

Heinzerling *et al.* mentioned some of the disadvantages of abdominal compression, including patient discomfort and decreased daily reproducibility of the compression effect based on abdominal contents, girth, and respiratory effort [5]. To the best of our knowledge, however, few studies have evaluated the impact of abdominal compression on the interfraction variation in lung tumor position in SBRT. Bissonnette *et al.* compared the interfractional changes in tumor motion amplitude over an SBRT course between patients with and without abdominal compression and reported the greatest variability in tumor motion amplitude in patients with abdominal compression [4]. However, only three of 12 patients who underwent 4D CT had abdominal compression in Bissonnette *et al.* Our results confirm the tendency reported by Bissonnette *et al.* in a larger series of patients, with the largest variance observed in the lateral and longitudinal directions in our study [Fig. 4(a) and (b)]. This can be explained by the restriction of motion in the vertical direction due to the compression effect. Indeed, the linear or highly elliptical path of the lung tumor trajectory, as described previously by Seppenwoolde *et al.*, is exacerbated in the lateral and longitudinal directions, which oppose the smallest resistance in patients treated with abdominal compression [18]. Conversely, in patients treated without

compression, the absence of a restriction to the excursion of the tumor in the vertical direction explains the larger interfraction variation,  $\Sigma$ , and  $\sigma$  observed in this group of patients compared to those treated with compression (TABLE II). The selection criteria, which include some medical reasons for the group of patients treated without abdominal compression, may have  
 275 influenced our results. However, we think that the larger interfraction variation,  $\Sigma$ , and  $\sigma$  in the vertical direction observed in patients treated without compression, and the small variance in the vertical direction in patients treated with compression, were mostly due to an external factor, the abdominal pressure pad, than an internal factor, the underlying medical condition of each patient.

Case *et al.* found no relationship between the amplitude of liver motion and the  
 280 magnitude of interfraction change in liver position [11, 12]. This may have been due to the range of tumor motion amplitude of the patients included in their studies (the range of amplitude was  $\leq 19$  mm). However, in our study, we included patients with a larger range of tumor motion amplitude (10–40 mm), and found a correlation between motion amplitude in the longitudinal direction and the 3D vector displacements of interfraction variation in patients treated without  
 285 abdominal compression. Conversely, the correlation was poor in patients treated with abdominal compression (Fig. 5). This was probably due to the fact that abdominal compression might have generated additional random positional errors, making it difficult to predict the range of interfraction variation in patients treated with compression.

Considering that 70% of the patients in our series had a tumor in the lower lobe, we also  
 290 sought to determine the influence of the proximity of the tumor respective to the diaphragm on interfraction variation. There was no correlation between the tumor-diaphragm distance and the mean vector displacement.

Ikushima *et al.* evaluated the changes in soft tissue tumor position during hypofractionated, in-room, CT-guided SBRT of lung cancer. They reported a trend in ITV

295 movement in any direction of more than 5 mm away from the original position from the first fraction to the last fraction in more than 20% of the patients. In their series, isotropic margins of 10 mm around the ITV were necessary to ensure adequate coverage of the interfractional target motion errors in all cases in the absence of a soft-tissue-based alignment [10]. In our study, the percentages of interfraction variation greater than 5 mm in patients without and with abdominal  
300 compression were 20.0% and 40.0%, respectively, and the 5 mm margin around the ITV was insufficient, particularly with the use of abdominal compression without soft tissue target matching. Both Ikushima *et al.* and our study underline the lack of accuracy of bony matching, whose reliability was worsened by the use of abdominal compression in our data and the need for an additional margin to account for the interfraction variation, with an increased risk of healthy  
305 tissue irradiation.

The dosimetric impact of the use of abdominal compression on irradiated lung tissue has been reported by several authors [17, 19]. Bouilhol *et al.* using 4D CT MIP imaging to delineate the target volume reported only a small gain in healthy lung tissue sparing in a subsample of four patients (three in the lower lobe and one in the upper lobe). However, we did not evaluate the  
310 dosimetric impact of the use of abdominal compression because of the small CBCT FOV; therefore, CBCT-based treatment planning was not feasible.

## Conclusion

315 Abdominal compression was effective for reducing the amplitude of tumor motion. However, in most of the patients in our study, the use of abdominal compression seemed to increase the interfraction variation in tumor position despite reducing lung tumor motion. The daily tumor position deviated more systematically from the tumor position in the planning CT

scan in the lateral and longitudinal directions in patients treated with abdominal compression  
320 compared to those treated without compression. Therefore, target matching is required to correct  
or minimize the interfraction variation.

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